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Standard physical profiles given to soldiers with thyrotoxicosis do not inform the command structure that the soldier may well have difficulty learning, concentrating on important decisions, and functioning in a command role. As a consequence, important command and control decisions are made by a soldier who may not be psychologically performing at her highest level. Our objective was to determine if beta-adrenergic blockade would significantly improve the cognitive dysfunction associated with thyrotoxicosis. Cognitive function was measured in twenty patients with thyrotoxicosis using the Stroop Color Word Test, Reitan Trailmaking test, and the Folstein Mini-mental status exam. Severity of thyrotoxicosis was assessed by physical examination and standard laboratory testing. Thyrotoxic patients demonstrated significant cognitive dysfunction on both the Stroop Color Word score and Reitan Trail B score. The degree of cognitive dysfunction did not correlate with physical exam manifestations of thyrotoxicosis or serum thyroid function tests. Beta-adrenergic blockade was not associated with a significant improvement in cognitive function beyond that predicted by the learning curve demonstrated by a euthyroid control group. Cognitive function returned to normal following definitive treatment. The command structure should be informed that the thyrotoxic soldier may have difficulty with cognitive decision making functions until the thyroid blood tests return to normal following definitive therapy.

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INTRODUCTION

Thyrotoxicosis is one of the most common endocrine disorders diagnosed in young women (1). It presents most commonly in the second and third decade of life and effects women eight times more frequently than men. Because of the relatively high prevalence of thyrotoxicosis in this age and gender distribution, we frequently diagnose and treat active duty soldiers with this condition. Unfortunately, thyrotoxicosis has generally been present for many months before a correct diagnosis is made. Because thyrotoxicosis is associated with abnormal behavior and thinking, the soldier may have received numerous counseling statements and even adverse action reports before an accurate diagnosis is made. Primary among the complaints of these young soldiers are poor memory, inability to concentrate, inability to learn new tasks, easy frustration, emotional liability, nervousness, and poor performance both at work and in schools(2-9). Unfortunately these psychological manifestations of thyrotoxicosis are much less appreciated by health care providers than are the obvious physiologic manifestations of the disease (tremor, heat intolerance, nervousness, tachycardia, palpitations, eye stare, proptosis, diarrhea, proximal muscle weakness and weight loss).

Once a diagnosis of thyrotoxicosis is made, the soldier is routinely started on beta-blocker therapy to improve her physiologic symptoms and prepare them for definitive therapy (radioactive iodine ablation of the thyroid, surgical thyroidectomy, or anti-thyroidal medications) (10). The soldier is placed on physical profile that limits her activity and field deployment status until she has been adequately treated and rehabilitated. These physical profiles do not inform the command structure that the soldier may well have difficulty learning, making new memories, concentrating on important decisions, and functioning in a command role. As a consequence, important command and control decisions are still being made by a soldier who may not be psychologically performing at her highest level. The potential to make poor decisions and endanger the lives of soldiers under their command may be greatly increased while the soldier is thyrotoxic.

While several studies have documented the presence of measurable cognitive dysfunction in thyrotoxicosis, little information is available regarding the precise time course of recovery of normal cognition following definitive therapy or the potential beneficial effect of beta-blocker therapy on cognitive function(2, 5-7, 9, 11-18). MacCrimmon *et al* demonstrated that measurable cognitive deficits were associated with the severity of thyroid toxicity. While elevated thyroid hormone levels had little effect on performance of tasks emphasizing motor and cognitive speed, it was associated with impaired performance on those tasks requiring concentration and memory (Reitan Trailmaking test, Color-Word test interference factor, and paired associates learning). Once the patients were euthyroid (ten months post therapy), all measurable cognitive deficits returned to normal.

Likewise, Robbins *et al* demonstrated that when a thyrotoxic patient was forced to consider more than one thing at a time, both problem-solving time and the number of errors made increased significantly

when compared to controls (11). Once again, all measurable cognitive deficits returned to normal once the patient was euthyroid.

Rockey *et al* extended these observations by using the Sickness Impact Profile to assess the effect of thyrotoxicosis on behavior (13). Patients reported that they were less productive and required more naps and rest periods than normal. Furthermore, they reported being more irritable, critical and demanding in social and family interactions than normal. All abnormalities returned to normal once euthyroid status was achieved.

Whybrow summarized the data available on the effects of thyrotoxicosis on cognition (8). He concluded that the majority of studies demonstrate intellectual dysfunction, impaired concentration, cognitive clouding, and tense dysphoria in thyrotoxic patients. All of these changes revert to normal once the euthyroid state is achieved following definitive therapy. However, the precise time course of this transition to normal thinking is unknown.

The hyperadrenergic state induced by excess thyroid hormone may be a major contributor to the cognitive dysfunction present in thyrotoxic patients (3, 4). The physiologic manifestations of thyrotoxicosis are the same as those seen in any condition in which the sympathetic nervous system (SNS) is activated (fear, nervousness, fight or flight response). Obviously, it would be difficult to learn, complete complex tasks or make important decisions while the sympathetic nervous system is stimulated. Therefore, it may be possible to improve cognitive function by using beta-blockers to blunt the effect of SNS hyperactivation induced by thyrotoxicosis.

Our hypotheses were: (1) Untreated thyrotoxicosis would be associated with marked abnormalities in cognitive function; (2) Marked improvement in cognitive function could be achieved with beta-blocker therapy; and (3) Cognitive deficits in thyrotoxicosis would be completely reversible once the soldier is rendered euthyroid following definitive therapy.

BODY

All patients referred to the Endocrine Clinic at Walter Reed Army Medical Center, Washington, DC for evaluation of thyrotoxicosis were consider for entry into this study. In order to select only those patients with Graves' Disease (thyrotoxicosis caused by hyperthyroidism), the following inclusion and exclusionary criteria were used.

Inclusionary Criteria

1. Clinical thyrotoxicosis arising from Graves' Disease.
2. Elevated thyroid hormone values (free T4) with a suppressed TSH (<0.2 mIU/L).
3. Nuclear medicine studies consistent with Graves' Disease.

Exclusionary Criteria

1. Subclinical hyperthyroidism
2. Subacute thyroiditis
3. Thyrotoxicosis arising from nodular thyroid disease
4. Atrial fibrillation
5. Known, symptomatic ASCAD
6. History of significant psychiatric disease
7. History of organic brain syndrome or dementia
8. Definitive therapy for thyrotoxicosis has been given
9. Contra-indications to beta-blocker therapy: asthma, bronchospasm, high grade heart block.
10. Pregnancy.

Outline

At the conclusion of the initial endocrine consultation by the primary author, informed consent was obtained from each patient eligible for participation in the study. Patients were taken to a quiet, comfortable room where each of the cognitive function tests were administered (Stroop Color-Word test, Reitan Trailmaking test, and Folstein Mini-Mental Status exam) by a single trained examiner.

In addition to the cognitive assessment, careful documentation of thyroid status was done using blood tests (ultrasensitive TSH, free thyroid hormone values) and quantifiable physical exam measurements including weight, heart rate, blood pressure, and tremor. Blood was drawn and allowed to clot in the collection tube, and centrifuged. The plasma was removed and frozen at -70C. Final batched assays will be run after the final patient completes the testing session 3 (euthyroid following definitive therapy). Free T4 and TSH values presented in this report were run individually in the nuclear medicine clinical assay department using a third generation Nichols chemiluminescent assay system.

Patients were treated for thyrotoxicosis in the usual manner with the choice of definitive therapy determined by the patient and their primary endocrinologist (usually the primary author). No effort was made to randomize patients to specific definitive treatment modalities.

Propanolol (Inderal) was given to each thyrotoxic subject using standard clinical guidelines at a dose of 40 mg every 6 hours. The propanolol was titrated every 48 hours until the pulse was less than 80 or a maximal dose of 120 mg every 6 hours was reached. If a patient was placed on a beta-blocker by the referring physician prior to our screening interview, our preference was to discontinue the beta-blocker for 48 hours prior to our baseline testing. For logistical reasons, some patients were unable to make numerous trips back to our facility for testing. In those few patients (n=5), the initial cognitive testing (Test 1) was done on beta-blockade and the second testing was done after discontinuation of beta-blockers for at least 48 hours. After this testing the patient was re-started on propanolol as described.

Subjects were instructed to take propanolol 1-2 hours prior to performing the cognitive function measures. This assured maximal anti-adrenergic activity of the propanolol at the time of testing.

Both psychiatric testing and physiologic assessment (including blood work) were done at three time points: (1) thyrotoxic, off beta-blockers for at least 48 hours, (2) after adequate beta-blockade as determined by heart rate less than 80 beats per minutes and absence of tremor, and (3) after definitive therapy, as soon as the patient was euthyroid following definitive therapy (surgery, RAI therapy, antithyroidal medications). All patients had thyroid function tests done monthly following definitive therapy. Patients were considered euthyroid once they had returned to a normal TSH and Free T4 after definitive therapy.

Control Group

An age and gender matched control group was recruited from the active duty personnel and support staff at Walter Reed Army Medical Center. The control group was used to define baseline normal scores and to quantify any learning that may develop with repeated administration of the cognitive instruments as used in this study. Control subjects were healthy without significant medical problems including no history of thyroid disease or use of thyroid medications. Cognitive function tests were administered in a manner identical to study subjects and matched for number of days between test one and test two. Control subjects were not give propanolol.

Instruments Used to Assess Cognitive Function

The Stroop Color-Word test assesses concentration as the subject must hold two concepts (word recognition and color recognition) in consciousness simultaneously. Scores reflect the number of correct responses per 45 second testing period for word recognition (black ink), color recognition (colored symbols) and color word score (identify the ink color that the word spells, not the color of ink it is printed in). These scores are then corrected for age using standard tables and used to calculated an interference

score (16A). Normal means for each score published previously are as follows: Word Score 108-120 correct responses per 45 seconds , Color Score 71-81 correct responses per 45 seconds , Color Word Score 41-51 correct responses per 45 seconds. Interference has a mean value of 0.0 (sd = 10) with subjects scoring above 0 classified as having "high resistance to interference "(16B).

The Reitan Trailmaking test assesses concentration ability. The test consist of two parts- A and B. In part A, subjects are asked to connect in numerical sequence circles numbered 1-25 following a small practice example. If errors are made, the subject is notified of the error and instructed to proceed so that errors count only against time. Performance is timed. Age related norms exist for comparison. Mean normal times for completion of Trail A range from 20-33 seconds (17,19,20)

In part B, there are 25 circles numbered 1-13 and lettered A-L. The subject is instructed to connect the circles while being timed. The subject must alternate between numbers and letters in ascending sequence for both. Again, errors are pointed out the subject who is then instructed to proceed. A mean of 58-87 seconds is considered a normal time range for completing Trail B(17).

The Folstein Mini-Mental Status exam is a 30-point gross screening tool which quickly assesses orientation , calculation, language, and short-term memory. This tool was used as a screen for short-term memory impairment. Patients are asked a ten-point date and place orientation, 3-point registration of three words, 5-point calculation exercise, 3-point recall exercise, and 9-point language exercises using a standard format (18).

Data Analysis

The primary response variables are the Trail Making Test Scores (measured in seconds), the Stroop Color-Word Scores (measured as number of correct responses per 45 seconds) and the mini-mental status exam (measured scale from 0 to 30). Data was analyzed using repeated measures analysis of variance. Data is presented as mean ± SEM. The correlation between psychological instrument scores and thyroid status (as determined by TSH, FT4, and pulse) for the hyperthyroid patients was examined using Spearman's correlation coefficient at each time point.

Results

Twenty patients with Graves' Disease meeting our study criteria were evaluated by the primary author between January 1996 and October 1996. Each of the patients signed informed consent and agreed to participate in the study. Four patients were transferred out of the area after completing the initial testing sessions (on beta-blockade and off beta-blockade) but before administration of the final euthyroid cognitive testing.

The mean size of the thyroid gland estimated by physical exam was 50 ± 13 gms. The mean 24 hour ^{131}I uptake was 62 ± 5% with a range of 28-76%. The Free T4 was elevated in all patient with a mean level at diagnosis of 85 ± 15 pMol/L (normal 10-30 pMol/L) . The serum TSH was less than 0.1

mIU/L in all patients. Choice of definitive therapy was as follows: radioactive iodine therapy n = 12, surgery n = 4, antithyroidal medications n = 4.

Comparison of demographic characteristics between thyrotoxic patients and controls revealed that they were well matched for age and gender (See Figure 1). Comparison of the physiologic measurements between thyrotoxic patients (off propanolol) and euthyroid controls revealed a significantly higher pulse (95 $\pm$ 5 vs 74 $\pm$ 2, p = 0.004) and systolic blood pressure (140 $\pm$ 5 vs 128 $\pm$ 3, p = 0.04) as well as a more common presence of a resting tremor (85% vs none, p = < 0.01).

A comparison of the initial cognitive function test results in euthyroid controls with thyrotoxic Graves' patients is given in Figure 2. Thyrotoxic patients demonstrated significantly more cognitive dysfunction on both the Reitan Trail B (75 $\pm$ 8 vs 57 $\pm$ 3 seconds to complete the trail, p = 0.03) and the Color Word Score (43 $\pm$ 1.5 vs 49 $\pm$ 3 correct responses/ 45 seconds, p = 0.04) than did the euthyroid controls. Furthermore, thyrotoxic subjects showed significantly more interference than euthyroid controls (-2 $\pm$ 1.4 vs 5.2 $\pm$ 3, p = 0.04).

Clinical parameters of pulse, blood pressure, and Free T4 were correlated with initial cognitive function scores shown to be significantly different between thyrotoxic patients and controls (Reitan Trail B, Color Word Score, Interference). None of the clinical parameters correlated significantly with these measures of cognitive function. Representative examples of the correlation of the Color Word Score with pulse and Free T4 are presented in Figure 3.

In the thyrotoxic patients, the mean time between cognitive function tests administered on propanolol and off propanolol was 8 $\pm$ 1 days (range 4-15 days) . Five thyrotoxic patients were on propanolol at test session 1, while the remaining 15 were on propanolol at test session 2. In order to quantify the magnitude of the learning curve, euthyroid controls were matched with thyrotoxic patients for number of days between cognitive function tests. The mean number of days between cognitive testing in the control group was 7 $\pm$ 1 days (p = NS compared with thyrotoxic patients).

The euthyroid controls showed a significant improvement in many of the cognitive function scores with repeated testing (See Figure 4). The calculated interference score tended to improve with repeat testing but this change did not achieve statistical significance.

Comparison of test session 1 with test session 2 in thyrotoxic patients without regard to treatment with propanolol revealed a significant positive learning curve for most of the parameters measured (See Figure 5). The magnitude of the improvement in cognitive function scores associated with repeat administration of the tests is given in Figure 6 for euthyroid controls and thyrotoxic subjects. The degree of improvement in each of the parameters did not differ significantly between euthyroid controls and thyrotoxic patients.

Representative changes between the scores from test session 1 and test session 2 are demonstrated in Figure 7A for Trail B and Color Word Score. Comparison of test 1 with test 2 after excluding patients on propanolol at test 1 (n=5) did not significantly change our results (See Figure 7B).

A dose of propanolol of 40-60 mg every six hours was required to maintain a resting pulse less than 80 beats per minute throughout the day. Administration of propanolol to the thyrotoxic patients was associated with a significant decline in pulse from 95 ± 5 to 73 ± 2 beats per minute ($p = < 0.001$) with resolution of tremor. There was no significant difference between the pulse and blood pressure of the thyrotoxic patients on propanolol with the control group at the time of testing.

Examining only the thyrotoxic patients, testing on propanolol was associated with a significant improvement in the Word Score (110 ± 4 vs 105 ± 4 correct responses/45 seconds, $p = 0.02$), Color Score (79 ± 3 vs 76 ± 3 correct responses/45 seconds, $p = 0.05$) , and Color Word Score (47 ± 2 vs 42 ± 2, correct responses/45 seconds, $p = 0.003$) with compared to testing without beta-blockade (See Figure 8). There was no significant improvement in the Trail B score or the interference score in response to beta-blockade.

A comparison of the degree of improvement on each of the cognitive tests in the control group between test session 1 and test session 2 with the thyrotoxic patients tested off propanolol and on propanolol is given in Figure 9. While the thyrotoxic patients consistently showed less improvement in scores on repeat testing than euthyroid controls, these differences did not achieve statistical significance. The changes in Trail B score (seconds to complete the trail) and Color Word Score (correct responses/45 seconds) are demonstrated in Figure 10 for both controls and thyrotoxic patients. Propanolol was not associated with an improvement in cognitive scores beyond that predicted by the learning curve of repeat testing within a short time interval.

At the time this report is being written, six thyrotoxic patients have returned to a euthyroid state following definitive therapy and have had the cognitive testing completed for a third time a mean of 3.3 months after the initial testing. In these 6 patients, scores for the Trail B test improved significantly over time from 85± 14 seconds at initial testing to 47 ± 4 seconds at final testing ($p = 0.04$). Furthermore, Color Word Scores improved significantly from 43 ± 4 at initial testing to 51 ± 3 at final testing as did the interference score (mean of 0 ± 1 at baseline, 5 ± 1.5 at final testing). These improvements brought each cognitive function score into the top normal range once the patients achieved the euthyroid state. Final repeat testing on the control group is still in progress.

Discussion

Thyrotoxicosis induced by Graves' Disease is associated with a significant, measurable impairment in cognitive function. Our data is consistent with prior reports of cognitive dysfunction in thyrotoxic patients (7, 11, 12). Graves' patients had a significantly more difficult time completing tasks that required two concepts to be maintained in consciousness concurrently as demonstrated by the difficulty completing the Color Word test that required simultaneous word recognition and color recognition. Likewise, thyrotoxic subjects demonstrated significant impairment in concentration as demonstrated by the significantly longer time needed to complete the Reitan Trail B test (alternate between numbers and letters in an ascending sequence).

While thyrotoxic subjects demonstrated a significant impairment in cognitive function, test scores were still within the lower range of normal as determined by larger population testing. However, when compared to age and gender matched euthyroid controls, cognitive function is significantly lower than would be expected. Furthermore, a marked improvement in cognitive function was seen once the patients return to the euthyroid state after definitive testing. Therefore, it appears that thyrotoxicosis is associated with a significant, reversible decline in cognitive performance in patients that develop Graves' Disease.

Because of the difficulty maintaining two concepts in the consciousness simultaneously, one would expect a clinically significant decline in work performance in thyrotoxic subjects whose job demands significant decision making or data analysis. The ability to decide between several alternatives is very likely to be impaired. Furthermore, impaired concentration would be expected to lead to an inability to complete tasks in an orderly fashion or to learn new duties. It is obvious that this type of cognitive function can significantly effect the ability of soldiers in leadership roles to complete their missions.

Since the cognitive function tests even while thyrotoxic are within the low normal range, a soldier with minimal decision making responsibility may be able to compensate for these impairments in cognitive function. However, soldiers in position of command and control who are required to function at maximum capacity during very stressful situations are likely to demonstrate a significant impairment in decision making skills. Fortunately, these cognitive function changes are reversible and return to a normal level at nearly the same time the soldier becomes euthyroid (about 3 months after definitive therapy). Prior studies had demonstrated that the cognitive function was reversible when cognitive tests were repeated 10-12 months after therapy, but this report is the first to document the recovery of cognitive function closely parallels the return of normal thyroid function blood tests approximately 3 months after definitive therapy.

Interestingly, the degree of cognitive dysfunction as measured by either the Reitan Trailmaking Test or Stroop Color Word test did not correlate degree of adrenergic activity (pulse, blood pressure) or thyroid hormone levels (Free T4 or TSH). Some of the thyrotoxic patients with the poorest color word scores had the lowest resting pulses. Likewise, very poor color word scores were seen in patients with only two fold elevations in free T4 levels. These findings are in contrast to the prior report of MacCrimmon et al who reported a significant association between elevation in total serum T4 and Stroop interference factor and

Spokes B score but no correlation with Spokes A, Stroop Reading time, Competing voices, or finger tapping measures (7). These differences are likely due to the difference in measurement of serum T4. The measurement of Free T4 used in this study more closely reflects thyroid status than older total T4 determinations that are influenced by numerous medical conditions and medications. A better assessment of association of cognitive function and thyroid status will be available once the serum free T4 and free T3 levels run in duplicate as a batch are available following the completion of this study.

However, our data emphasize that clinicians need to be aware that significant cognitive dysfunction may be present with only minimal signs and symptoms of adrenergic hyperactivity. Furthermore, the lack of correlation between cognitive function tests and clinical manifestations of adrenergic activity suggests that cognitive dysfunction in thyrotoxicosis is not associated with adrenergic hyperactivity and therefore may not improve with beta-adrenergic blockade.

This study is unique in that it is the first to examine the effect of beta-adrenergic blockade on cognitive function. The cognitive function test used in this study were chosen because they were reported to have minimal if any improvement with repeated testing. However, it is clear that re-administration of the cognitive tests within a week of initial testing was associated with a significant improvement in scores in both euthyroid controls and thyrotoxic patients. The analysis was complicated because five patients were taking propanolol at the time of test session 1 while the remaining 15 subjects were taking propanolol at test session 2. Careful analysis of the data with respect to sequence and treatment effect revealed only a significant sequence effect (improvement in second testing) and no difference with respect to propanolol therapy. Furthermore, analysis of the data excluding the 5 subjects on propanolol at test session 1 did not alter our results or conclusions. Therefore, we are confident that the improvement in scores demonstrated in the first two testing sessions of this study were the result of a learning curve associated with repeated administration of the cognitive tests within a week of the initial testing and not an effect of beta-adrenergic blockade.

It is clear from our data that while beta adrenergic blockade with propanolol induces a significant improvement in the physiological status of the patient, it is not associated with a significant improvement in cognitive function. Administration of propanolol in doses sufficient to mask all signs of hyperadrenergic activity did not improve the cognitive function tests scores beyond that expected from the learning curve of repeat testing.

Because of the significant learning curve, it was decided not to administer the tests monthly following definitive therapy as was originally planned in order to determine when cognitive function had returned to normal. Instead, serum thyroid function tests were monitored monthly until a clinically relevant endpoint was reached: return of thyroid function tests to normal range (TSH and Free T4). By repeating the cognitive tests only one additional time many months following the initial testing we hoped to minimize any further learning curve and still provide new information regarding the time course of recovery of cognitive function.

As can be seen in the initial 6 subjects that have completed final testing, a marked improvement in cognitive function scores was seen at the time the thyroid blood tests have returned to normal (mean 3 months following definitive therapy). Once euthyroid, the cognitive test scores are consistently in the high normal range for all tests administered. This data suggests that recovery of normal cognitive function occurs early in the resolution of thyrotoxicosis and is present once normal thyroid function tests are attained following definitive therapy. Final cognitive function in the control group is still ongoing.

In summary, it is important to emphasize the need for psychological profile in addition to a physical profile for soldiers diagnosed with Graves' Disease. Clinicians must be aware the severity of cognitive dysfunction does not correlate with physical exam signs of heart rate and tremor or with degree of elevation of thyroid hormones. Furthermore, the marked improvement in sense of well being, tremor, and heart rate associated with beta-blockade does not signify an improvement in cognitive function. Cognitive dysfunction is most likely to be manifest in soldiers required to examine several alternatives and arrive at a plan of action. Fortunately, a return to normal cognitive function can be expected within 3-4 months of definitive therapy. The findings of this study will allow health care personnel to provide better advice regarding the prevalence, severity, and time course of impaired cognitive performance in soldiers with Graves' Disease.

CONCLUSIONS

Major Findings:

1. Cognitive dysfunction is present and can be readily measured in patients with Graves' Disease.
2. The severity of cognitive dysfunction cannot be predicted from clinical examination signs or serum thyroid function tests.
3. The cognitive dysfunction demonstrated in Graves' Disease does not appear to be induced by the hyper-adrenergic state of the patient for the following reasons:
   A. No correlation of cognitive dysfunction with signs of hyperadrenergic state.
   B. No improvement in cognitive function in response to adequate beta-adrenergic blockade.
4. Following definitive treatment for Graves' Disease, cognitive function returns to normal once serum thyroid function tests normalize.

Implications:

1. The commanders of soldiers with Graves' Disease should be informed that their soldier has a reversible impairment in cognitive function. This impairment in cognitive function is most likely to be made manifest in soldiers in positions of leadership, command and control. The decision making ability of soldiers with Graves' Disease in positions of leadership should be carefully monitored by superiors. Soldiers demonstrating significant impairments in decision making should be relieved of decision making responsibility until thyroid blood tests have returned to normal (about 3 months). Once thyroid blood tests have returned to normal, soldiers can resume all normal duties without limitations.

2. Health care workers need to be reminded that the severity of thyrotoxicosis as determined by physical examination and routine thyroid blood tests do not predict the degree of cognitive dysfunction. Therefore, information regarding both physical and psychological performance of the soldier while thyrotoxic should be passed on to the soldiers superior in the form of a profile.

3. While beta- blockers such as propanolol provide significant improvement in the physiologic manifestations of thyrotoxicosis, they do not improve cognitive function. Commanders and health care workers need to be reminded that while beta-blockers significantly improve the soldiers appearance and sense of well being, they do not necessarily improve his cognitive performance.

4. The cognitive dysfunction present in thyrotoxicosis is generally mild and always reversible with 3-4 months of definitive therapy. Therefore, after adequate treatment soldiers can resume productive military careers with limitations.

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Figure 1.

CLINICAL CHARACTERISTICS: CONTROLS vs THYROTOXIC SUBJECTS

Characteristic	Subjects n = 20	Controls n = 20	p
Age (yrs)	41 ± 3	38 ± 2	NS
Gender	15 F : 5 M	15 F : 5 M	NS
Pulse	95 ± 5	74 ± 2	0.004
Systolic	140 ± 5	128 ± 3	0.04
Diastolic	69 ± 2	73 ± 2	NS
Tremor present at rest	85%	None	< 0.01

Figure 2

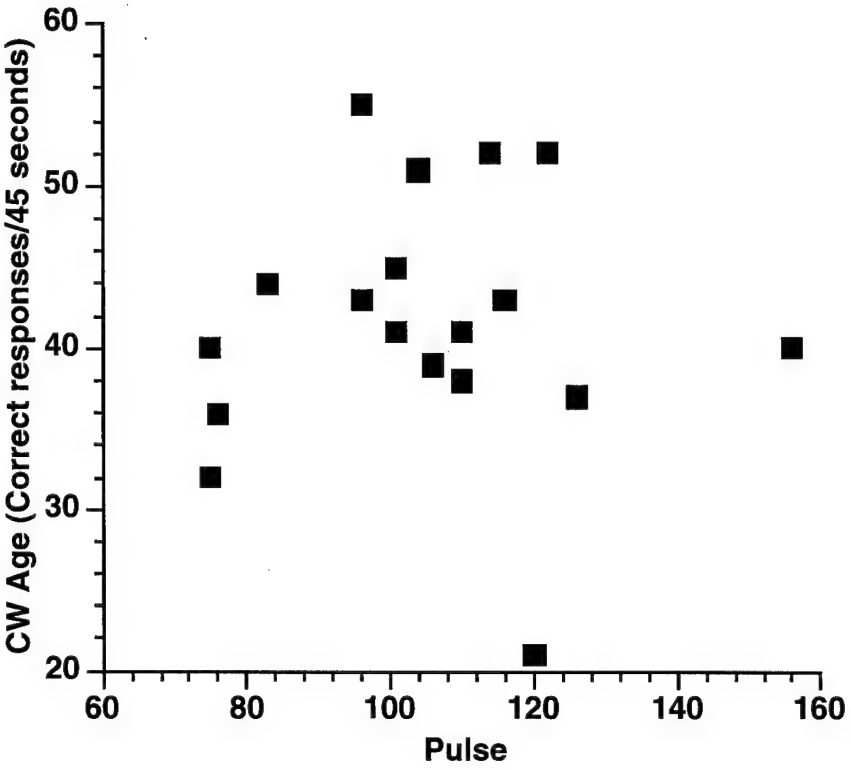
EUTHYROID CONTROLS vs THYROTOXIC SUBJECTS

Test	Euthyroid Controls	Thyrotoxic Subjects	p
MMSE Score	29 ± 0.2	29 ± 0.2	NS
Trail A (seconds)	29 ± 2	35 ± 4	NS
Trail B (seconds)	57 ± 3	75 ± 8	0.03
Word Score (Correct Responses/45 sec)	111 ± 3	107 ± 5	NS
Color Score (Correct Responses/45 sec)	75 ± 2	77 ± 2	NS
Color Word Score (Correct Responses/45 sec)	49 ± 3	43 ± 1.5	0.04
Interference	5.2 ± 3	-2 ± 1.4	0.04

Figure 3

CORRELATION OF COLOR WORD SCORE

With Pulse



With Free T4

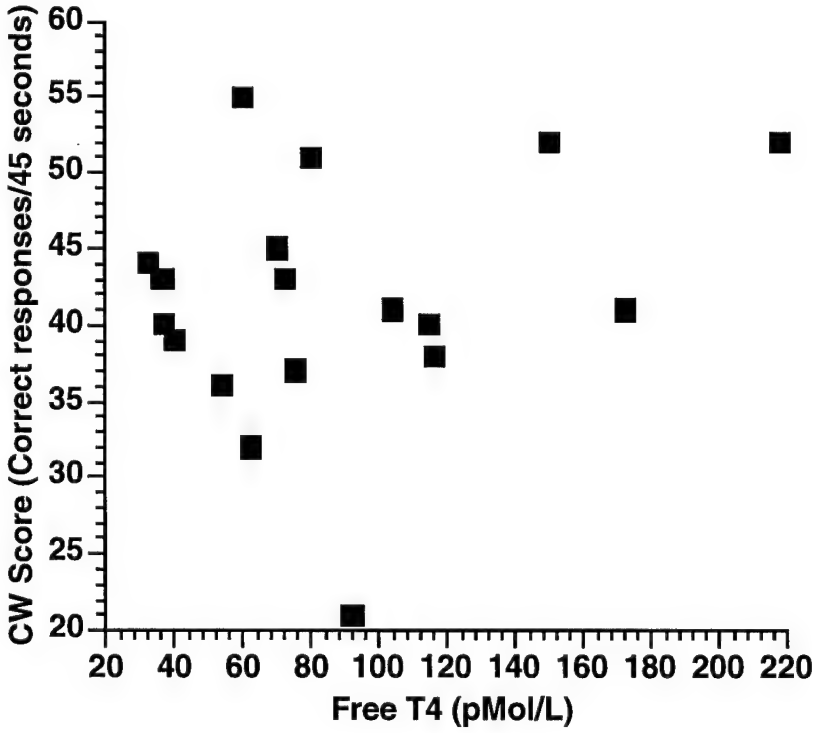


Figure 4

EUTHYROID CONTROLS: TEST 1 VS TEST 2

Test	First Test	Second Test	p
MMSE Score	29 ± 0.2	29 ± 0.2	NS
Trail A (seconds)	29 ± 2	24 ± 2	0.004
Trail B (seconds)	57 ± 3	46 ± 4	0.002
Word Score (Correct Responses/45 sec)	111 ± 3	119 ± 3	0.006
Color Score (Correct Responses/45 sec)	75 ± 2	83 ± 3	0.003
Color Word Score (Correct Responses/45 sec)	49 ± 3	56 ± 2	0.02
Interference	5.2 ± 3	7.9 ± 2	NS

Figure 5

THYROTOXIC SUBJECTS: TEST 1 VS TEST 2

Test	First Test	Second Test	p
MMSE Score	29 ± 0.2	29 ± 0.3	NS
Trail A (seconds)	35 ± 4	26 ± 1.6	0.005
Trail B (seconds)	75 ± 8	61 ± 6	0.01
Word Score (Correct Responses/45 sec)	107 ± 5	108 ± 4	NS
Color Score (Correct Responses/45 sec)	77 ± 2	78 ± 3	0.006
Color Word Score (Correct Responses/45 sec)	43 ± 1	46 ± 2	0.004
Interference	-2 ± 1.5	1 ± 1.5	0.04

Figure 6

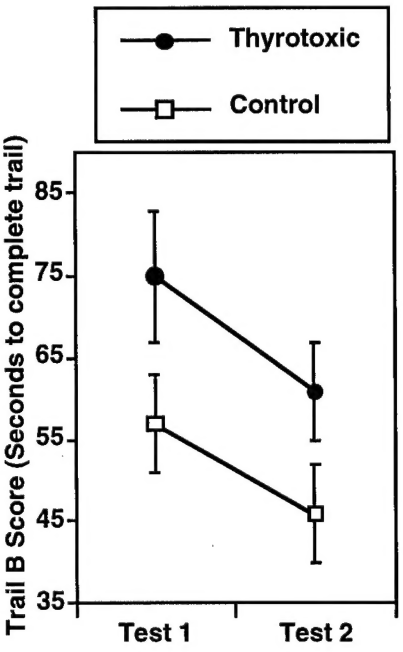
SUMMARY TABLE FOR IMPROVEMENT IN SCORES

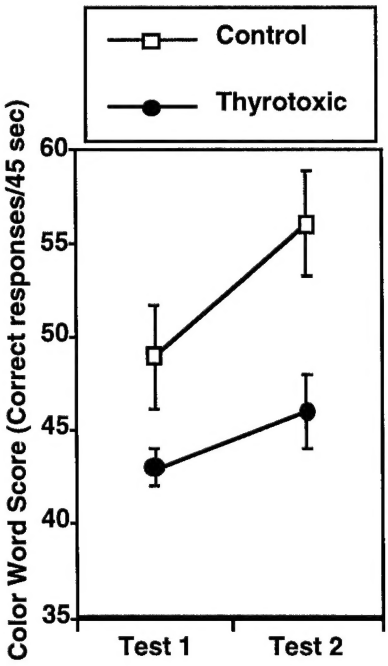
Test	PERCENT IMPROVEMENT Controls Test 1 vs Test 2	 Subjects Test 1 vs Test 2
MMSE Score	0%	0%
Trail A	17%	26%
Trail B	19%	19%
Word Score	7%	1%
Color Score	11%	1%
Color Word Score	14%	7%
Interference	52%	150%

Figure 7

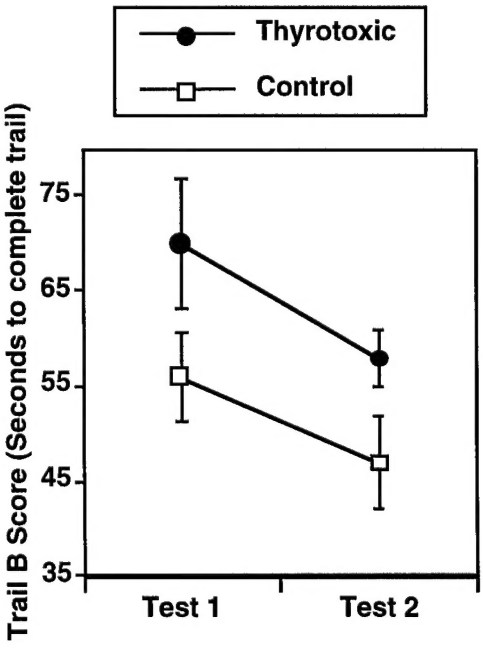
Comparison Test 1 vs Test 2

7A. Controls vs All Thyrotoxic Subjects





7B. Controls vs Thyrotoxic Subjects Not on Inderal At Test 1



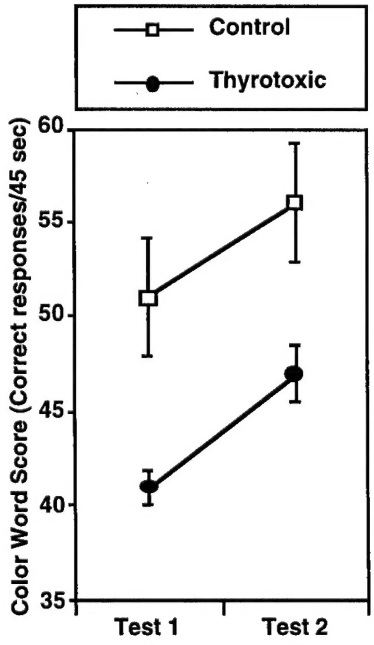


Figure 8

THYROTOXIC SUBJECTS: Off beta blockers vs on beta blockers

Test	Off Inderal	On Inderal	p
MMSE Score	29 ± 0.2	29 ± 0.3	NS
Trail A (seconds)	32 ± 3	29 ± 3	NS
Trail B (seconds)	71 ± 7	66 ± 7	NS
Word Score (Correct Responses/45 sec)	105 ± 4	110 ± 4	0.02
Color Score (Correct Responses/45 sec)	76 ± 3	79 ± 3	0.05
Color Word Score (Correct Responses/45 sec)	42 ± 2	47 ± 2	0.003
Interference	-2 ± 1.5	1.2 ± 1.6	0.12

Figure 9

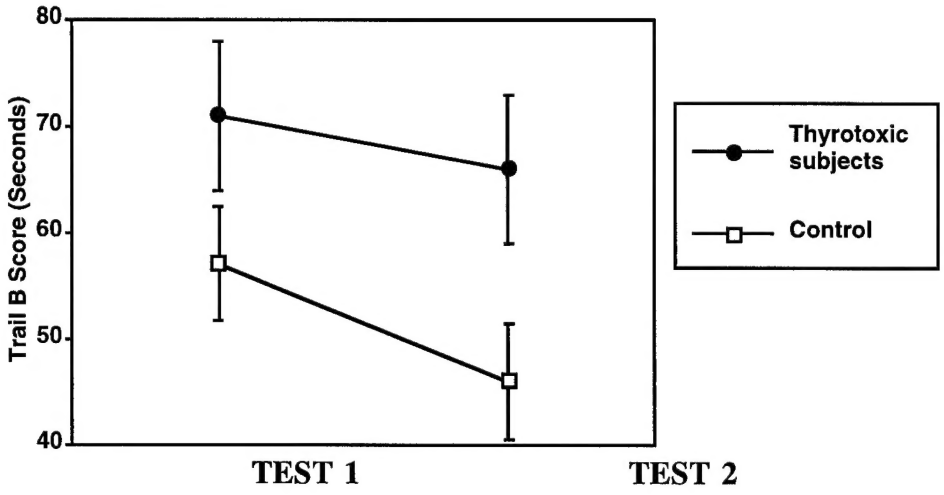
SUMMARY TABLE FOR IMPROVEMENT IN SCORES

	PERCENT IMPROVEMENT	
Test	**Controls Test 1 vs Test 2**	**Subjects Off vs On inderal**
MMSE Score	0%	0%
Trail A	17%	9%
Trail B	19%	7%
Word Score	7%	5%
Color Score	11%	4%
Color Word Score	14%	12%
Interference	52%	151%

Figure 10

EFFECT OF INDERAL ON THYROTOXIC SUBJECTS vs CONTROL GROUP

TRAIL B TEST



COLOR WORD SCORE